REMARKS

Claims 7, 13 and 22 have been amended as set forth in the above complete listing of the claims. Claim 15 has been cancelled. Upon entry, claims 7-8, 10-14, 22, and 23 will be pending.

Regarding the Amendments

The specification has been amended at page 16, paragraph 0037 to delete an embedded hyperlink and/or other form of browser-executable code by removing the "www". As such, the amendment merely addresses a formality and does not add new matter.

Please cancel claim 15 without prejudice or disclaimer.

Claim 7 has been amended to recite a cellular proliferative disease "associated with pancreatic cancer or colorectal cancer." The amendment is supported, for example, at page 23, paragraph 0056. Further, claim 7 has been amended to clarify that the abbreviation "ppENK" and by reciting "a preproenkephalin (ppENK) gene" and merely addresses a formality. As such, the amendments do not add new matter.

Claim 13 has been amended to clarify the subject matter regarded as the invention. The claim is supported by claim 13 as originally filed. As such, the amendment does not add new matter.

Claim 22 has been amended to correct a typographical error. As such, the amendment does not add new matter.

Regarding the Restriction Requirement

Applicants acknowledge the election of Group II and the human preproenkaphalin A gene. Applicants further acknowledge the Examiner's withdrawal of the restriction requirement for the specific primer pair in view of Applicant's preliminary amendment. As such, claims 7-8, 10-15, 22, and 23 are currently under consideration.

Regarding the Objection

The Examiner has objected to the use of an embedded hyperlink and/or other form of browser-executable code in the specification. It is noted in the Office Action that removing the "www", thereby deleting the embedded hyperlink and/or browser-executable code, would be remedial. In accordance with the Examiner's suggestion, Applicants have requested amendment to paragraph 0037 of the specification as set forth above in the "amendments" section. This amendment does not add any new matter, but merely corrects an informality. As such, removal of the objection is respectfully requested.

The Examiner has objected to claim 22 as containing a misspelling. The claim has been amended, thereby changing the misspelled word "methd" to the intended correct spelling "method." Accordingly, Applicants respectfully request removal of the objection to claim 22.

Rejection Under 35 U.S.C. § 112

The rejection of claims 7-8, 10-15, and 22 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed.

It is acknowledged in the Office Action that the specification is enabling for a method for detecting a cellular proliferative disorder associated with pancreatic cancer or colorectal cancer. It is alleged, however, that the specification provides no guidance for detecting any cellular proliferative disorders besides pancreatic cancer or colorectal cancer. As such, it is alleged that undue experimentation would have been required for one skilled in the art to practice the claimed methods. Applicants respectfully traverse the rejection for the reasons set forth below.

Applicants submit that there is no reason to believe that the exemplified method of detecting the cellular proliferative disorders of pancreatic cancer or colorectal cancer would not similarly be effective with respect to other types of cellular proliferative disorders. As such, and absent objective evidence to the contrary, it is submitted that one skilled in the art, viewing the specification, reasonably would have believed that identifying aberrant methylation of regions of the ppENK gene or regulatory region thereof, in a nucleic acid-containing specimen from a subject, would be indicative of a cellular proliferative disease, including proliferative diseases in cells other then pancreatic or colorectal cancer cells. The claimed methods of identifying a cellular proliferative disease are based on the ability of hypermethylation to affect the expression of genes having methylated regions (see, for example, page 11, paragraph 0028). The specification discloses that the ppENK gene encodes an opioid growth factor, or [Met5]-enkephalin, and that is a negative regulator of cell growth with tumor suppressor functions (see, for example, page 11, paragraph 0029). As such, in view of the specification, which exemplifies methods of identifying a cellular proliferative disorder, for example, pancreatic cancer and colorectal cancer, the skilled artisan would have known that identifying aberrant methylation of regions of the ppENK gene or regulatory region is indicative of a cellular proliferation disorder, regardless of the tissue origin.

Further in this respect, Applicants submit that the negative growth regulatory effects of opioid growth factor are known in connection with multiple cell proliferative diseases. For example, Zagon et. al. (Int J Oncol. 1999 Mar; 14(3): 577-84, a copy of which is attached as Exhibit A) disclose that the opioid peptide [Met5]-enkephalin, encoded by ppENK, is constitutively expressed, autocrine produced, and capable of suppressing cell replication in various kinds of cancers, including pancreatic cancer. McLaughlin et. al. (Int J Oncol. 1999 Mar; 14(5): 991-8, a copy of which is attached as Exhibit B) describe growth inhibition of human squamous cell carcinoma of the head and neck by [Met5]-enkephalin. Furthermore, Maneckjee et. al. (Cell Growth Differ. 1994 Oct; 5(10): 1033-40, a copy of which is attached as Exhibit C), teach that opioids such as ppENK effectively induce cell death and apoptosis in lung cancer cell lines. Applicants point out that Zagon et. al. and Maneckjee et. al. are cited in the current specification at page 11, paragraph 0029. Thus, the results reported by Zagon et. al., McLaughlin et. al., and Maneckjee et. al. confirm that, as disclosed in the subject application, ppENK has important growth regulatory effects in multiple tissue types and can be associated with various cellular proliferative diseases. As such, Zagon et. al., McLaughlin et. al., and Maneckjee et. al. provide confirmatory evidence that the methods can be practiced as claimed.

In summary, specification discloses a method of detecting a cellular proliferative disorder in a subject by identifying aberrant methylation of regions of the ppENK gene or regulatory region, and exemplifies the claimed methods using pancreatic and colorectal cancer cells. Further, Zagon et. al., McLaughlin et. al., and Maneckjee et. al. provide objective evidence that, as of the earliest priority date of the subject application, one skilled in the art would have known that altered ppENK activity is capable of effecting cell replication in various kinds of cell proliferative diseases. As such, the skilled artisan, viewing the subject application, reasonably would have known that identifying aberrant methylation of regions of the ppENK gene or regulatory region, in a nucleic acid-containing

specimen from a subject, would be useful in detecting various cellular proliferative diseases, including pancreatic or colorectal cancer.

Nonetheless, claim 7 has been amended in order to advance prosecution, thereby rendering the rejection moot. Accordingly, it is respectfully requested that the Examiner reconsider and remove the rejection of the claims under 35 U.S.C. § 112, first paragraph.

The rejection of claims 7-8, 10-15, and 22 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite is respectfully traversed.

Specifically, the Examiner required that the full name for the abbreviation "ppENK" be recited in the claim. Claim 7 has been amended in accordance with the Examiner's suggestion. Accordingly, it is respectfully requested that this rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

CONCLUSION

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Acct. No. 50-1355.

Respectfully submitted,

Date: February 13, 2004

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Enclosures: Exhibits A, B and C

Exhibit A

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1: Int J Oncol. 1999 Mar;14(3):577-84. Related Articles, Links

Human pancreatic cancer cell proliferation in tissue culture is tonically inhibited by opioid growth factor.

Zagon IS, Smith JP, McLaughlin PJ.

Department of Neuroscience and Anatomy, H-109, The Pennsylvania State University, The M.S. Hershey Medical Center, Hershey, PA 17033, USA.

Pancreatic adenocarcinoma is a fatal malignancy that ranks as the fourth most common cause of cancer-related mortality in the United States. The median survival after diagnosis is 3-6 months, with a 5-year survival rate of 3% or less. In spite of treatment efforts of surgery, radiation, and chemotherapy, the survival rate remains unchanged. In this study, we discovered that an endogenous opioid peptide, [Met5]-enkephalin, inhibited the growth of human pancreatic cancers in vitro; in view of this pentapeptide's action it has been termed opioid growth factor (OGF). OGF was found to be constitutively expressed, autocrine produced, and tonically capable of suppressing cell replication in an opioid receptor mediated manner. Growth inhibition was dose-related, reversible, not cytotoxic, and independent of serum. All 4 pancreatic cancer cell lines examined, representative of poor to well-differentiated neoplasias, exhibited growth regulation by OGF. Immunocytochemical studies detected both OGF and its related receptor, zeta, in the cytoplasm of log phase cells. Radioimmunoassays revealed that OGF was produced and secreted by the cells. These data suggest that a native opioid peptide, OGF, interacts with a novel opioid receptor, zeta, to arrest the growth of human pancreatic cancer.

PMID: 10024694 [PubMed - indexed for MEDLINE]

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1: Int J Oncol. 1999 May;14(5):991-8. Related Articles, Links

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Regulation of human head and neck squamous cell carcinoma growth in tissue culture by opioid growth factor.

McLaughlin PJ, Levin RJ, Zagon IS.

Department of Neuroscience and Anatomy, H109, Milton S. Hershey Medical Center, Hershey, PA 17033, USA.

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common malignancy worldwide. Approximately half of the patients afflicted die within 5 years of diagnosis, and surviving patients may be left with severe esthetic and functional compromise. In this study, we discovered that an endogenous opioid peptide, [Met5]-enkephalin, inhibited the growth of human SCCHN in vitro; in view of this pentapeptide's action it has been termed opioid growth factor (OGF). OGF was found to be a constitutively expressed, receptor-mediated growth inhibitory agent that appears to be autocrine produced and secreted. Growth regulation was dose-related, reversible, cytostatic, and independent of serum. All 6 human SCCHN cell lines examined exhibited growth modulation by OGF. Blockade of peptide-receptor interaction by opioid antagonists (naltrexone), or addition of antibody to OGF, resulted in substantial increases in cell number compared to control levels, showing the tonic nature of OGF-zeta activity. Immunocytochemical studies detected both OGF and its related receptor, zeta, in these cells, correlating with earlier findings of peptide and receptor in specimens of SCCHN obtained at surgery. These data suggest that a native opioid peptide, OGF, interacts with a novel opioid receptor, zeta, to tonically arrest the growth of human SCCHN.

PMID: 10200353 [PubMed - indexed for MEDLINE]

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1: Cell Growth Differ. 1994 Oct;5(10):1033-40. Related Articles, Links

Opioids induce while nicotine suppresses apoptosis in human lung cancer cells.

Maneckjee R, Minna JD.

Simmons Cancer Center, Department of Medicine, University of Texas Southwestern Medical Center, Dallas 75235-8590.

Previously, we have shown that opioids acting via specific receptors inhibit the growth of human lung cancer cells while nicotine, acting through nicotinic acetylcholine receptors, reverses this inhibition. Therefore, we studied the role of apoptosis in these processes. Treatment of human lung cancer cells with 0.1-1 microM morphine or methadone resulted in morphological changes and cleavage of DNA into nucleosome-sized fragments characteristic of apoptosis. Quantitation of DNA fragmentation showed that a dose-dependent increase occurred within 2 h of opioid treatment and was blocked by the antagonist naloxone. The apoptotic effect of opioids was suppressed by nicotine, while the nicotinic acetylcholine receptor antagonists, hexamethonium and decamethonium, reversed this suppression. In contrast, sphingosine, a protein kinase C inhibitor, caused significant DNA fragmentation which was not suppressed by nicotine. Unexpectedly, the combination of hexamethonium and opioids or hexamethonium and nicotine stimulated apoptosis. We found that nicotine, like phorbol 12-myristate 13-acetate, increased total protein kinase C (PKC) activity, while morphine and sphingosine decreased PKC activity, and nicotine reversed morphine inhibition of PKC activity. In contrast, methadone unexpectedly increased PKC activity. These results indicate that engagement of opioid receptors in human lung cancer cells induces apoptosis, while engagement of nicotine receptors suppresses apoptosis, which in some cases appear to be working through a PKC pathway. They also suggest complexities in the system where blockade of C6 or C10 nicotinic receptors can lead to facilitation of apoptosis. These findings suggest new strategies for treatment and prevention of cancer using opioids or nicotine receptors antagonists and are consistent with the idea that nicotine functions as a tumor promoter.

PMID: 7848904 [PubMed - indexed for MEDLINE]

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